BABEŞ-BOLYAI UNIVERSITY
Faculty of Mathematics and Computer Science

Analysis of Some Mathematical Models of Cell Dynamics in Hematology

Asist. Dr. Lorand Gabriel Parajdi
Joint work with my Ph.D. supervisor, Prof. Dr. Radu Precup

Department of Mathematics, "Babeș-Bolyai" University Cluj-Napoca, Romania

CSDCU-MIF
22-24 October 2020

Contents of the Thesis

- **Chapter 3**
  Optimization Problems in Chronic Myeloid Leukemia
  - 3.1 The optimization problem
  - 3.2 Optimal personalized dosing of a selective drug
  - 3.3 Non-specific drug optimization problem
  - 3.4 Optimal personalized dosing of a selective drug based on the extended model to terminally differentiated cells

- **Chapter 4**
  Mathematical Modeling of Stem Cell Transplantation in CML
  - 4.1 The mathematical model
  - 4.2 Existence and uniqueness of solutions
  - 4.3 Steady states and stability
  - 4.4 Numerical simulations

- **Conclusions and Further Research**
- **Appendix**
- **Bibliography**

Chapter 2: Mathematical Modeling of Chronic Myeloid Leukemia

The Chronic Myeloid Leukemia

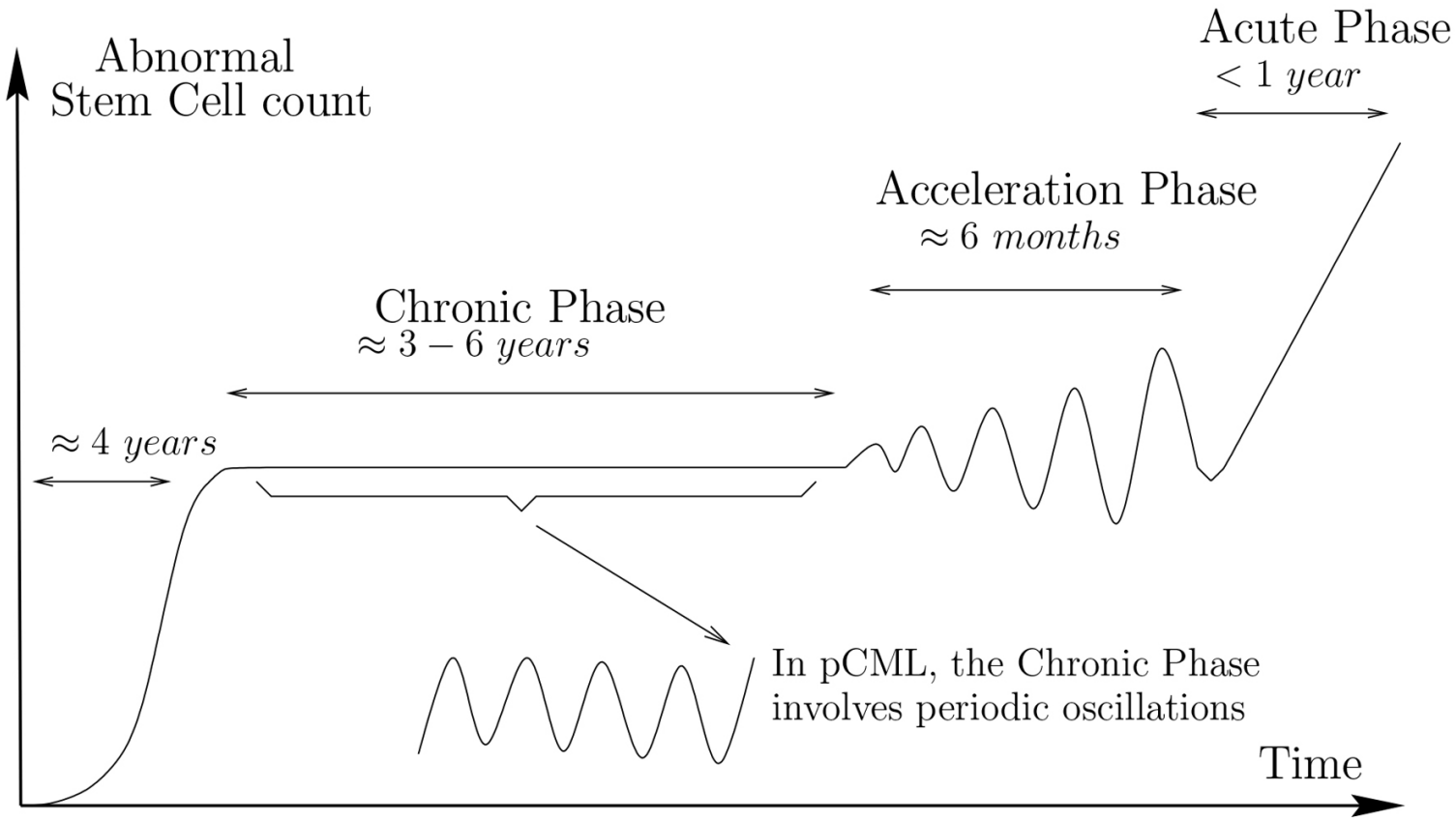


Figure: There are three distinct phases of CML.

Introduction

Starting from the paper of Dingli and Michor (2006), a mathematical model given by a two – dimensional differential system is introduced to understand the transition process from normal hematopoiesis to chronic and accelerated-acute stages in myeloid leukemia.

We assume that at each time t, the stem cell population divides into two:

- the normal stem cell population $x(t)$,
- the abnormal stem cell population $y(t)$.

The basic mathematical model

We study the following mathematical model:

$$\begin{cases} \frac{dx}{dt} = \frac{a}{1+b_1x+b_2y}x - cx \\ \frac{dy}{dt} = \frac{A}{1+B(x+y)}y - Cy. \end{cases} \quad (1)$$

Here the model parameters:

- a and A are the nonrestrictive growth rates of normal and abnormal stem cells;
- b_1, b_2, and B are the bone marrow microenvironment sensitivities;
- c and C are the death rates of normal and abnormal stem cells.
- The terms $\frac{1}{1+b_1x+b_2y}$ and $\frac{1}{1+B(x+y)}$ model the crowding effect in the bone marrow microenvironment, introduce competition between normal and abnormal stem cells and guarantee the homeostasis at the level of cell population.

We assume that for both cell populations, the growth rate is greater than the death rate, that is

$$a > c \quad \text{and} \quad A > C.$$

In order to reflect the advantage of the abnormal cells of being less sensitive to the bone marrow microenvironment, we assume that

$$b_1 \geq b_2 > B.$$

An alternative model for normal-abnormal dynamics can be found in the paper of Neiman (2000), A Mathematical Model of Chronic Myelogenous Leukemia.

- The case $b_1 = b_2$ was considered by Dingli and Michor (2006) and Cucuianu and Precup (2010). In this case, there are only two non-zero steady states

$$(d, 0) \quad \text{and} \quad (0, D)$$

where d and D represent the homeostatic amounts of normal and abnormal stem cells and are given by

$$d := \frac{1}{b_1}\left(\frac{a}{c} - 1\right) \quad \text{and} \quad D := \frac{1}{B}\left(\frac{A}{C} - 1\right) \tag{2}$$

- In our case, for system (1), we assume that $b_1 > b_2$. As we shall see, besides the non-zero steady states $(d, 0)$ and $(0, D)$ there could also exist a third steady state

$$(x^*, y^*)$$

where $x^* > 0$ and $y^* > 0$.

Existence, uniqueness, continuous dependence on data and boundedness of solutions

Theorem: (Existence and uniqueness)

For any $t_0 \geq 0$ and $u_0 = (x_0, y_0) \in (0, +\infty)^2$, there is a unique saturated solution $u = u(\cdot, t_0, u_0) = (x, y)$ of system (1) which is defined on the whole semiline $[t_0, +\infty)$, is of class C^∞, with $x > 0$ and $y > 0$ on $[t_0, +\infty)$, and satisfies the initial condition

$$u(t_0) = u_0.$$

Theorem: (Boundedness of solutions)

The solution $u = u(\cdot, t_0, u_0)$ is bounded on $[t_0, +\infty)$ for every $t_0 \geq 0$ and $u_0 \in (0, +\infty)^2$.

Continuous dependence on data

Let $u = (x, y)$ be the unique saturated solution of (1) satisfying the initial condition $u(t_0) = u_0$, where $t_0 \geq 0$ and $u_0 = (x_0, y_0) \in (0, +\infty)^2$, and let $v = (\overline{x}, \overline{y})$ be any solution of a Cauchy problem of the form

$$\begin{cases} v' = g(t, v) \\ v(t_0) = v_0, \end{cases} \tag{3}$$

where $v_0 = (\overline{x}_0, \overline{y}_0) \in \mathbb{R}^2_+$, $g = (g_1, g_2) \in C\left([t_0, t_0 + h] \times \mathbb{R}^2_+; \mathbb{R}^2_+\right)$, and it is assumed that v exists on the interval $[t_0, t_0 + h]$.
We are interested to estimate the functions $x - \overline{x}$ and $y - \overline{y}$ in terms of the differences $x_0 - \overline{x}_0$, $y_0 - \overline{y}_0$, $f_1 - g_1$ and $f_2 - g_2$, where

$$\begin{aligned} f_1(x, y) &= \frac{ax}{1 + b_1 x + b_2 y} - cx, \\ f_2(x, y) &= \frac{Ay}{1 + B(x + y)} - Cy. \end{aligned}$$

By direct computation, we can show that f_1, f_2 satisfy the Lipschitz conditions

$$\begin{aligned}
|f_1(w_1, w_2) - f_1(\overline{w}_1, \overline{w}_2)| &\leq l_{11}|w_1 - \overline{w}_1| + l_{12}|w_2 - \overline{w}_2|, \\
|f_2(w_1, w_2) - f_2(\overline{w}_1, \overline{w}_2)| &\leq l_{21}|w_1 - \overline{w}_1| + l_{22}|w_2 - \overline{w}_2|,
\end{aligned}$$

with

$$\begin{aligned}
l_{11} &= \max\{a - c, c\}, & l_{12} &= \frac{ab_2}{4b_1} \\
l_{21} &= \frac{A}{4}, & l_{22} &= \max\{A - C, C\}
\end{aligned}$$

Denote

$$l = \max\{l_{11}, l_{12}\} + \max\{l_{21}, l_{22}\}.$$

Theorem:

Assume that

$$\begin{aligned} |f_1(w_1, w_2) - g_1(t, w_1, w_2)| &\leq \eta_1 \\ |f_2(w_1, w_2) - g_2(t, w_1, w_2)| &\leq \eta_2 \end{aligned}$$

for all $w_1, w_2 \in \mathbb{R}_+$, $t \in [t_0, t_0 + h]$, and some numbers $\eta_1, \eta_2 \geq 0$. Then

$$|x(t) - \overline{x}(t)| + |y(t) - \overline{y}(t)| \leq [|x_0 - \overline{x}_0| + |y_0 - \overline{y}_0| + (\eta_1 + \eta_2)\, h]\, e^{hl}$$

for all $t \in [t_0, t_0 + h]$.

Remark:

Component-wise estimates are also possible using the method based on vector-valued norms and matrices.

Steady states

A steady state, an equilibrium, or a stationary solution of system (1), is a constant solution, i.e., a solution for which $dx/dt = dy/dt = 0$. Thus, the steady states of (1) are obtained by solving the algebraic system

$$\frac{ax}{1 + b_1 x + b_2 y} - cx = 0, \tag{4a}$$

$$\frac{Ay}{1 + B(x + y)} - Cy = 0. \tag{4b}$$

The solutions of the system (4a)-(4b) are the couples

$$(0, 0), \quad (d, 0), \quad (0, D) \quad \text{and} \quad (x^*, y^*),$$

where d, D are given by (2),

$$x^* = -\frac{b_2 c(A - C) - BC(a - c)}{BCc(b_1 - b_2)} \quad \text{and} \quad y^* = \frac{b_1 c(A - C) - BC(a - c)}{BCc(b_1 - b_2)}.$$

Local stability of steady states

Theorem: (Local stability of steady states)

(a) If $D < d$, then $(d, 0)$ is the only one steady state which is locally asymptotically stable.
(b) If $b_1 > b_2$ and $d < D < (b_1/b_2)d$, then (x^*, y^*) is the only one steady state which is locally asymptotically stable.
(c) If $D > (b_1/b_2)d$, then $(0, D)$ is the only one steady state which is locally asymptotically stable.

Remark:

In all of the three cases of the previous theorem, the steady state $(0, 0)$ is unstable as can be shown based on the assumptions $a > c$ and $A > C$.

Global stability

Theorem: (Global asymptotic stability of steady states)

For any positive saturated solution $u = (x, y)$ of system (1), one has:

$$
\begin{aligned}
&(i) \quad u(t) \to (d, 0) \quad \text{as} \quad t \to +\infty, \quad \text{in case} \quad D < d; \\
&(ii) \quad u(t) \to (x^*, y^*) \quad \text{as} \quad t \to +\infty, \quad \text{in case} \quad d < D < (b_1/b_2)\, d; \\
&(iii) \quad u(t) \to (0, D) \quad \text{as} \quad t \to +\infty, \quad \text{in case} \quad (b_1/b_2)\, d < D.
\end{aligned}
$$

Numerical simulation of the model

Parameter estimations

We can find a parameter estimation in the paper of Dingli and Michor (2006), where it is estimated that the total number of stem cells in a healthy adult body is approximately

$$d = 2 \times 10^4.$$

The stem cells divide every 200 days and die every 500 days. Therefore, the growth and death rates of normal stem cells (per capita per day) are

$$a = \frac{1}{200} = 0.005 \qquad \text{and} \qquad c = \frac{1}{500} = 0.002.$$

We can determine the bone marrow microenvironment sensitivity of normal stem cells from the following relationships

$$b_1 = \frac{\frac{a}{c} - 1}{d} = 0.75 \times 10^{-4} \text{ and } b_2 = \frac{b_1}{2} \approx 0.38 \times 10^{-4}.$$

Parameters A, B and C vary from patient to patient, and so D.

Case when $a < A$, $b_1 > b_2 > B$ and $c < C$.

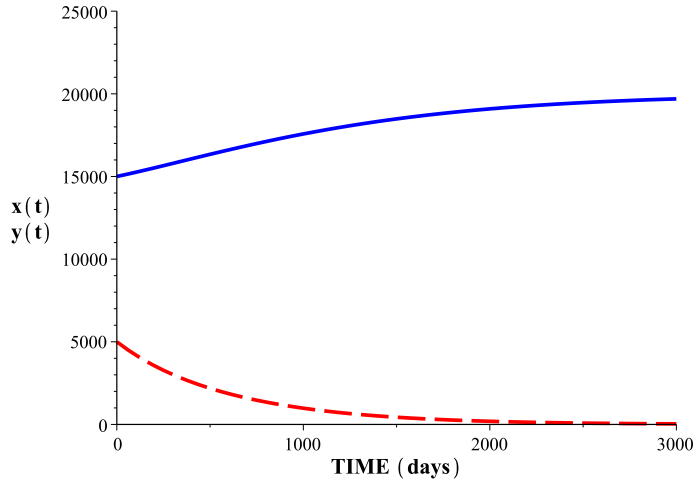


Figure: Behavior of the normal and leukemic stem cell populations in Case I, for the following values: $a = 0.005$, $b_1 = 0.75 \times 10^{-4}$, $b_2 = 0.38 \times 10^{-4}$, $c = 0.002$, $A = 0.01$, $B = 0.19 \times 10^{-4}$, $C = 0.009$, with initial conditions: $x(0) = 1.5 \times 10^4$ and $y(0) = 5 \times 10^3$.

In the normal hematopoietic state ($D < d$), in time ($T = 3000$ days), the normal stem cell population $x(t)$ (blue solid line) tends to the value d while the leukemic stem cell population $y(t)$ (red broken line) tends towards 0.

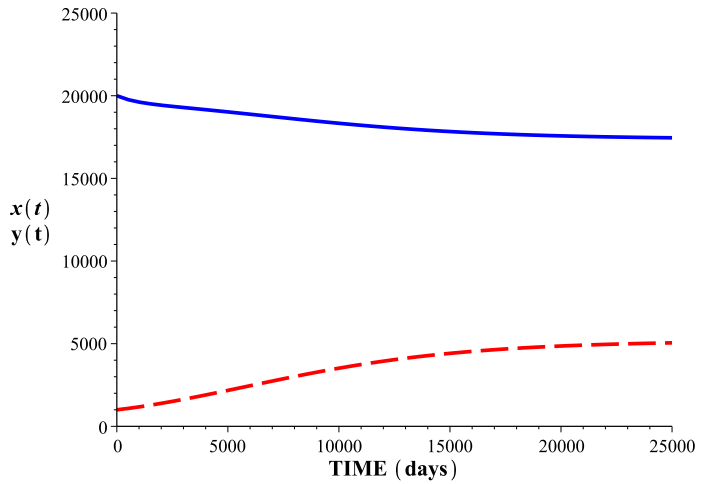


Figure: Behavior of the normal and leukemic stem cell populations in Case I, for the following values: $a = 0.005$, $b_1 = 0.75 \times 10^{-4}$, $b_2 = 0.38 \times 10^{-4}$, $c = 0.002$, $A = 0.01$, $B = 0.19 \times 10^{-4}$, $C = 0.007$, with initial conditions: $x(0) = 2 \times 10^4$ and $y(0) = 1 \times 10^3$.

In the CP-CML state, $(d < D < \frac{b_1}{b_2} d)$, in time $(T = 25000$ days), the normal and leukemic stem cell populations, denoted by: $x(t)$ and $y(t)$ tend toward x^* and y^*, respectively.

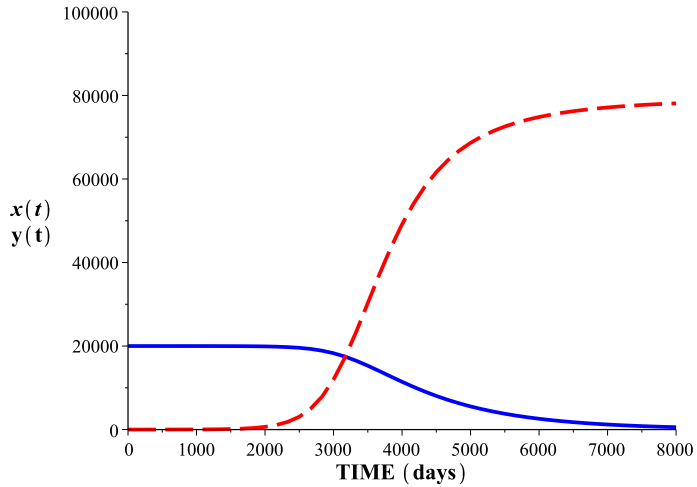


Figure: Behavior of the normal and leukemic stem cell populations in Case I, for the following values: $a = 0.005$, $b_1 = 0.75 \times 10^{-4}$, $b_2 = 0.38 \times 10^{-4}$, $c = 0.002$, $A = 0.01$, $B = 0.19 \times 10^{-4}$, $C = 0.004$, with initial conditions: $x(0) = 2 \times 10^4$ and $y(0) = 1$.

In the AAP-CML state, $(\frac{b_1}{b_2} d < D)$, in time ($T = 8000$ days), the normal stem cell population $x(t)$ (blue solid line) tends towards 0 while the leukemic stem cell population $y(t)$ (red broken line) tends to the value D.

The extended model to terminally differentiated cells

Working at the level of primitive stem cells, there is not a common way to determine the size of the two (normal and abnormal) cell populations.

This idea first appears in F. Michor et al. (2005), and applied to our mathematical model yields the extended system of eight equations

$$
\begin{array}{llll}
x_1'(t) = \frac{a_1 x_1}{1+b_1 x_1+b_2 y_1} - c_1 x_1 & \text{(NSC)} & y_1'(t) = \frac{A_1 y_1}{1+B(x_1+y_1)} - C_1 y_1 & \text{(ASC)} \\
x_2'(t) = a_2 x_1 - c_2 x_2 & \text{(NPC)} & y_2'(t) = A_2 y_1 - C_2 y_2 & \text{(APC)} \\
x_3'(t) = a_3 x_2 - c_3 x_3 & \text{(NDC)} & y_3'(t) = A_3 y_2 - C_3 y_3 & \text{(ADC)} \\
x_4'(t) = a_4 x_3 - c_4 x_4 & \text{(NTC)} & y_4'(t) = A_4 y_3 - C_4 y_4 & \text{(ATC).}
\end{array}
$$

Here $x_2(t)$, $y_2(t)$ stand for the normal (N) and abnormal (A) progenitor cell (PC) populations; $x_3(t)$, $y_3(t)$ stand for the normal and abnormal differentiated cell (DC) populations; and $x_4(t)$, $y_4(t)$ stand for the normal and abnormal terminally differentiated cell (TC) populations, respectively.

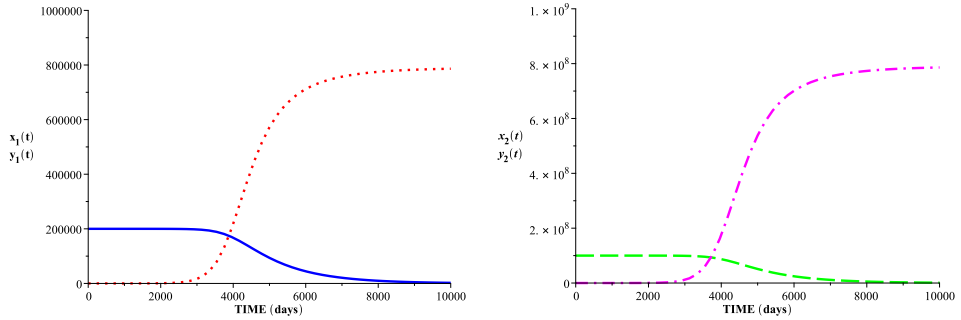
In the equilibrium state, assuming that in a healthy adult the number of stem cells is $d = x_1^* = 2 \times 10^5$, the number of progenitor cells is $x_2^* = 1 \times 10^8$, the number of differentiated cells is $x_3^* = 1 \times 10^{10}$ and the number of terminally differentiated cells is $x_4^* = 1 \times 10^{12}$ (see F. Michor et al. (2005)).
Note that if

$$(x_{1E},\ y_{1E})$$

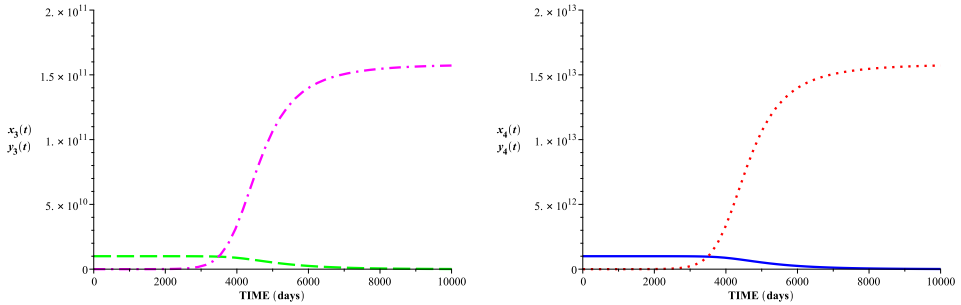
is any equilibrium (E) of the initial system (1), then

$$(x_{1E},\ y_{1E},\ a_2x_{1E}/c_2,\ A_2y_{1E}/C_2,\ a_2a_3x_{1E}/c_2c_3,\ A_2A_3y_{1E}/C_2C_3,$$
$$a_2a_3a_4x_{1E}/c_2c_3c_4,\ A_2A_3A_4y_{1E}/C_2C_3C_4)$$

is an equilibrium of the extended system, and the two equilibria have the same stability property.



(a) Stem cell populations (b) Progenitor cell populations



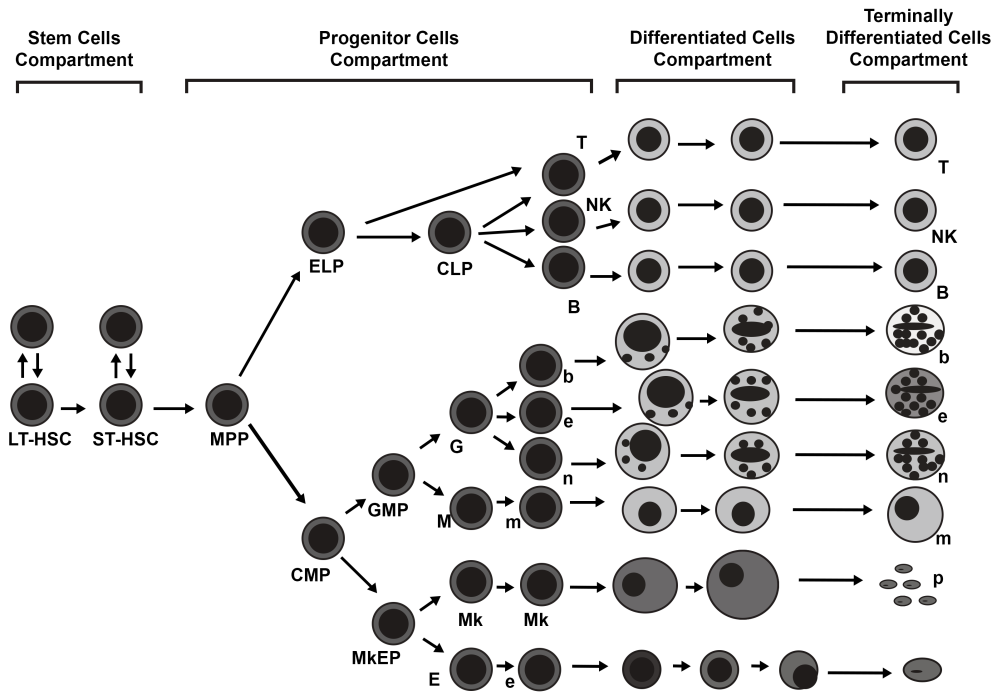
(c) Differentiated cell populations (d) Terminally differentiated cell populations

Figure: Behavior of (a) stem cell populations, (b) progenitor cell populations, (c) differentiated cell populations and (d) terminally differentiated cell populations for the parameter values: $a_1 = 0.005$, $a_2 = 4$, $a_3 = 5$, $a_4 = 100$, $b_1 = 0.75 \times 10^{-5}$, $b_2 = 0.38 \times 10^{-5}$, $c_1 = 0.002$, $c_2 = 0.008$, $c_3 = 0.05$, $c_4 = 1$, $A_1 = 0.01$, $A_2 = 8$, $A_3 = 10$, $A_4 = 100$, $B = 0.19 \times 10^{-5}$, $C_1 = 0.004$, $C_2 = c_2$, $C_3 = c_3$, $C_4 = c_4$, and initial conditions: $x_1(0) = 2 \times 10^5$, $x_2(0) = 1 \times 10^8$, $x_3(0) = 1 \times 10^{10}$, $x_4(0) = 1 \times 10^{12}$, $y_1(0) = y_2(0) = y_3(0) = y_4(0) = 1$.

Chapter 3: Optimization Problems in Chronic Myeloid Leukemia

The optimization problem

Although model (1), has been built to describe the dynamics in the compartment of stem cells, it can be equally used for any other class of hematopoiesis, either of progenitor or precursor cells. Of course, the "death" rates include the transition rates to the next layer, while the growth rates depend on the cell proliferation in the previous compartment.



We shall perform the analysis under the assumption of chronic leukemia state (CML state):

$$d < D < \frac{d}{s},$$

where $s = \frac{b_2}{b_1}$ and we have a third equilibrium $[x^*, y^*]$ where:

$$x^* = (\frac{1}{s} - 1)^{-1}(\frac{d}{s} - D) \text{ and } y^* = (1 - s)^{-1}(D - d). \tag{5}$$

Next we consider the ration $\frac{y^*}{x^*}$, from (5) we have:

$$\frac{y^*}{x^*} = \frac{1}{s}\frac{D-d}{\frac{d}{s}-D}. \tag{6}$$

Alternatively, one may consider the ratio:

$$\beta = \frac{y^*}{2x^*+y^*}. \tag{7}$$

which may be put into connection with routine laboratory assays (such as the BCR-ABL percentage).

From (2) we know that:

$$d = \frac{1}{b_1}\left(\frac{a}{c} - 1\right) \text{ and } D = \frac{1}{B}\left(\frac{A}{C} - 1\right).$$

Any therapy directed at tumor cells should decrease D and this happens by increasing the death and sensitivity parameters C and B and by decreasing the growth rate A.

We apply the same idea for normal cells, and we obtained the following formulas:

$$D_m = \frac{1}{v_2 B}\left(v_1 \frac{A}{C} - 1\right), \; d_m = \frac{1}{v_4 b_1}\left(v_3 \frac{a}{c} - 1\right) \text{ and } s_m = v_5 s$$

where

$$v_1, v_4 \leq 1, \; v_2, v_3 \geq 1 \text{ and } v_5 < \frac{1}{s}.$$

We assume that a drug S which modifies all the kinetic parameters is available, and assume that the **total dose/toxicity/cost** associated to the therapy is given by the formula:

$$J = p_1 \left(\frac{1}{v_1} - 1\right)^{\theta_1} + p_2 (v_2 - 1)^{\theta_2} + p_3 (v_3 - 1)^{\theta_3} + p_4 \left(\frac{1}{v_4} - 1\right)^{\theta_4} + p_5 (v_5 - 1)^{\theta_5}. \tag{8}$$

Here the exponents $\theta_1, \theta_2, \theta_3, \theta_4, \theta_5 \in \mathbb{R}_+$ give the rapidity of the growth of J as $\frac{1}{v_1}, v_2, v_3, \frac{1}{v_4}, v_5$ increase to infinity and the parameters p_1, p_2, p_3, p_4 and p_5 are proportionality factors of **dosage/toxicity/cost**.

In particular, we can consider the expression

$$J = p_1 \left(\frac{1}{v_1} - 1\right) + p_2 (v_2 - 1) + p_3 (v_3 - 1) + p_4 \left(\frac{1}{v_4} - 1\right) + p_5 (v_5 - 1), \tag{9}$$

or its quadratic version. The problem is to find the factors $v_1, ..., v_5$ such that the total **dose/toxicity/cost** is minimal and the patient state is under a desired value.

Optimal personalized dosing of a selective drug

According to the chosen estimation indicator, we consider three different optimal problems:

(1) Optimal personalized dosing of a selective drug:

From the mathematical expression (7) of the BCR-ABL percentage β, the ration $\frac{y^*}{x^*} = \frac{2\beta}{1-\beta}$. Next, using (6), where s is assumed to be $s < 1$ (for example we choose s to be $1/2$), one obtains the value of D:

$$D = (1 + \beta)d,$$

and we consider a drug which acts only on the proliferation rate A. The expression of D, where B is known, gives patient's relativ proliferation rate $\rho = A/C$,

$$\rho = 1 + (1 + \beta)Bd.$$

After diagnosis, the patient is treated with a standard dose J_0 and the response is assessed T months later by the new BCR-ABL β_0, which as above, gives after-treatment relative proliferation rate

$$\rho_0 = 1 + (1 + \beta_0)Bd.$$

Thus, after treatment, the patient's relative proliferation rate ρ has been modified by the factor $v_0 = \frac{\rho_0}{\rho}$.
Now from the expression of one drug dose given by:

$$J = p\left(\frac{1}{v} - 1\right)^{\theta} \text{ where } \theta \in \mathbb{R}_+,$$

we can find the proportionality dosage factor p, namely:

$$p = \frac{J_0}{\left(\frac{1}{v_0} - 1\right)^{\theta}} = J_0\left(\frac{1+(1+\beta_0)Bd}{(\beta-\beta_0)Bd}\right)^{\theta}.$$

At this stage, we are able to prescribe the personalized dose of the drug for a given target $\beta_* = 0.05\%$, at T months after reaching a new equilibrium:

$$J_1 = J_0 \left(\frac{(\beta - \beta_*)(1+(1+\beta_0)Bd)}{(\beta - \beta_0)(1+(1+\beta_*)Bd)} \right)^{\theta}.$$

It remains to make a choice for the exponent θ. If a maximal dose J_{max} is prescribed in the case of an admissible response to the standard dose J_0 equal to $(\beta_* + \beta)/2$, where it is consider that the drug is inefficient and thus it has to be replaced if the response is up to $(\beta_* + \beta)/2$.

With J_{max} instead of J_1 and $(\beta_* + \beta)/2$ in the place of β_0 and taking the logarithm, we obtain

$$\theta = \frac{ln(J_{max}/J_0)}{ln\ \gamma}$$

where

$$\gamma = \frac{2+(2+\beta_*+\beta)Bd}{1+(1+\beta_*)Bd}.$$

Non-specific drug optimization problems

(2) First non-specific drug optimization problem:

In this first non-specific drug problem we consider that the ratio between the modified and the initial leukemic homeostatic values D_m and D is under a chosen number $q < 1$, and the ratio between the modified and the initial normal homeostatic values d_m and d is larger than some given number $r > 1$, that is:

$$D_m \leq qD \text{ and } d_m \geq rd.$$

We assume that no modification is given to the relative sensitivity parameter s, hence $v_5 = 1$, which guarantees the condition $D_m \leq s^{-1} d_m$. For the first non-specific drug scenario, the toxicity/dose function is:

$$J = p_1(\frac{1}{v_1} - 1) + p_2(v_2 - 1) + p_3(v_3 - 1) + p_4(\frac{1}{v_4} - 1),$$

and finding the parameters v_1, v_2, v_3 and v_4 means to solve the constrained convex optimization problem:

$$\textit{Minimize } J$$
$$\textit{Subject to } \varphi_i(\nu) \leq 0,\ i = 1, .., 6,$$

where $\nu = (v_1, v_2, v_3, v_4) \in {\mathbb{R}_+}^4$,

$$\varphi_1(\nu) = v_1 - 1,\ \varphi_2(\nu) = 1 - v_2,$$
$$\varphi_3(\nu) = v_1 \frac{A}{BC} - v_2 q \left(\frac{A}{BC} - \frac{1}{B} \right) - \frac{1}{B},$$
$$\varphi_4(\nu) = 1 - v_3,\ \varphi_5(\nu) = v_4 - 1,$$
$$\varphi_6(\nu) = -v_3 \frac{a}{b_1 c} + v_4 r \left(\frac{a}{b_1 c} - \frac{1}{b_1} \right) + \frac{1}{b_1}.$$

To solve the problem, we use the Kuhn-Tucker Theorem. Let $L(\nu, u)$ be the Lagrangian associated to the convex optimization problem:

$$L(\nu, u) = J(\nu) + \langle u, \varphi(\nu) \rangle,$$

where $u \in \mathbb{R}^6_+$, $\varphi(\nu) = (\varphi_1(\nu), ..., \varphi_6(\nu))$ and $\langle u, \varphi(\nu)\rangle = u_1\varphi_1(\nu) + ... + u_6\varphi_6(\nu)$.

Then a solution of the optimization problem is a point $\nu \in \mathbb{R}^4_+$ for which there is $u \in \mathbb{R}^6_+$ such that the couple u, ν is a saddle point of the Lagrangian, that is a solution of the following system:

$$\nabla_\nu L(\nu, u) \geq 0, \tag{10}$$
$$\langle \nu, \nabla_\nu(\nu, u)\rangle = 0, \tag{11}$$
$$\nabla_u L(\nu, u) \leq 0, \tag{12}$$
$$\langle u, \nabla_u(\nu, u)\rangle = 0. \tag{13}$$

Assume that $\nu_i \neq 1$ for $i = 1, ..., 4$, meaning that the first four parameters are all effectively altered. Since

$$\nabla_u L(\nu, u) = (v_1 - 1,\ 1 - v_2,\ v_1\frac{A}{BC} - v_2 q(\frac{A}{BC} - \frac{1}{B}) - \frac{1}{B},$$
$$1 - v_3,\ v_4 - 1,\ -v_3\frac{a}{b_1 c} + v_4 r(\frac{a}{b_1 c} - \frac{1}{b_1}) + \frac{1}{b_1}),$$

from (12) and (13), we find

$$u_1 = u_2 = u_4 = u_5 = 0,$$

while from the first two conditions (10) and (11) we obtained,

$$\begin{aligned} -\frac{p_1}{v_1^2} + u_3\frac{A}{BC} &= 0, \\ p_2 - u_3 q\left(\frac{A}{BC} - \frac{1}{B}\right) &= 0, \\ p_3 - u_6\frac{a}{b_1 c} &= 0, \\ -\frac{p_4}{v_4^2} + u_6 r\left(\frac{a}{b_1 c} - \frac{1}{b_1}\right) &= 0. \end{aligned}$$

Solving yields

$$u_3 = \frac{p_2 BC}{q(A-C)},\ u_6 = \frac{p_3 b_1 c}{a},\ v_1 = \left(\frac{p_1 q(A-C)}{p_2 A}\right)^{\frac{1}{2}},\ v_4 = \left(\frac{a p_4}{p_3 r(a-c)}\right)^{\frac{1}{2}}.$$

Finally, since $u_3 \neq 0$ and $u_6 \neq 0$, using again the first two conditions (10) and (11), we obtain the optimal solution:

$$v_1 = \left(\frac{p_1 q(A-C)}{p_2 A}\right)^{\frac{1}{2}}, \quad v_2 = \frac{\left(\frac{p_1 qA(A-C)}{p_2}\right)^{\frac{1}{2}} - C}{q(A-C)},$$
$$v_3 = \frac{\left(\frac{p_4 ra(a-c)}{p_3}\right)^{\frac{1}{2}} + c}{a}, \quad v_4 = \left(\frac{ap_4}{p_3 r(a-c)}\right)^{\frac{1}{2}}.$$

Despite the above analytical solution, a numerical one is possible and easy to obtain by using Matlab, Maple, or Mathematica computer software.

(3) Second non-specific drug optimization problem:

This second multi-parameterd scenario uses a similar approach to the previous one, but this time the response is evaluated interms of y^*/x^* which is controllably decreased, more exactly

$$\frac{y_m^*}{x_m^*} \leq k\frac{y^*}{x^*} \quad \text{and} \quad D_m < \frac{d_m}{s_m},$$

where $\frac{y^*}{x^*}$ and $\frac{y_m^*}{x_m^*}$ are the indicators before and after treatment, respectively, and $k < 1$ is a target coefficient.

To this aim one has to minimize the functional J given by (9) under the constraints

$$v_1 \leq 1, \ v_2 \geq 1, \ v_3 \geq 1, \ v_4 \leq 1 \text{ and } v_5 < \frac{b_1}{b_2}.$$

Numerical simulations for the objective function (9):

Case (a):				
v_1	v_1	v_3	v_4	J_{min}
0.94868	1.38157	2.99807	0.96225	1.72330
1	1.66666	2.99807	0.96225	1.75256
1	1.66666	3.10000	1	1.75333
1	1.66666	1	0.22222	3.08333

Case (b):				
v_1	v_2	v_3	v_4	J_{min}
0.94868	1.38157	2.99807	0.96225	1.72330
0.88000	1	2.99807	0.96225	1.78286
0.88000	1	3.10000	1	1.78363
0.88000	1	1	0.22222	3.11363

Case (c):				
v_1	v_2	v_3	v_4	J_{min}
0.94868	1.38157	2.99807	0.96225	1.72330
0.94868	1.38157	1	0.22222	3.05407
1	1.66666	1	0.22222	3.08333
0.88000	1	1	0.22222	3.11363

Case (d):				
v_1	v_2	v_3	v_4	J_{min}
0.94868	1.38157	2.99807	0.96225	1.72330
0.94868	1.38157	3.10000	1	1.72407
1	1.66666	3.10000	1	1.75333
0.88000	1	3.10000	1	1.78363

TABLE 2. First optimization problem: Numerical simulations with the parameters values $p_1 = 10$, $p_2 = 2$, $p_3 = 0.2$, $p_4 = 0.5$, $q = 0.6$ and $r = 4.5$.

Looking at the column giving the minimal toxicity/dose/cost J_{min}, we note an increase of toxicity/dose/cost when as we decrease the number of kinetic parameters targeted by the drug.

Optimal personalized dosing of a selective drug based on the extended model to terminally differentiated cells

We consider the following extended mathematical model:

$$x_1'(t) = \frac{a_1 x_1}{1+b_1 x_1+b_2 y_1} - c_1 x_1 \quad \text{(NSC)} \qquad y_1'(t) = \frac{A_1 y_1}{1+B(x_1+y_1)} - C_1 y_1 \quad \text{(ASC)}$$

$$x_2'(t) = a_2 x_1 - c_2 x_2 \quad \text{(NPC)} \qquad y_2'(t) = v_0 A_2 y_1 - C_2 y_2 \quad \text{(APC)}$$

$$x_3'(t) = a_3 x_2 - c_3 x_3 \quad \text{(NDC)} \qquad y_3'(t) = v_1 A_3 y_2 - C_3 y_3 \quad \text{(ADC)}$$

$$x_4'(t) = a_4 x_3 - c_4 x_4 \quad \text{(NTC)} \qquad y_4'(t) = A_4 y_3 - C_4 y_4 \quad \text{(ATC).}$$

we assume that the drug acts over the parameters A_2 and A_3 (see F. Michor et al. (2005)). Note that the effect over other parameters of Imatinib and of other used drugs, is not clarified in the literature.

Simulation of the optimal personalized dose formula:

BCR-ABL of untreated patient	BCR-ABL after standard dose $[0.01\% - 0.1\%]$	BCR-ABL the target value $< 0.01\%$	J_{max} maximum dose	J_0 initial standard dose	J_1 optimal dose
$\beta = 99\%$	$\beta_0 = 0.09\%$	$\beta_* = 0.005\%$	800 mg	400 mg	518.78 mg
$\beta = 96\%$	$\beta_0 = 0.05\%$	$\beta_* = 0.005\%$	800 mg	400 mg	492.00 mg
$\beta = 99\%$	$\beta_0 = 0.04\%$	$\beta_* = 0.005\%$	800 mg	400 mg	482.27 mg
$\beta = 98\%$	$\beta_0 = 0.03\%$	$\beta_* = 0.005\%$	800 mg	400 mg	469.93 mg
$\beta = 97\%$	$\beta_0 = 0.09\%$	$\beta_* = 0.005\%$	800 mg	400 mg	518.74 mg

Conclusion:

The same results are obtained in case that the drug acts only on A_2 which is the rate at which APC are produced from ASC. If we consider for one drug dose, the following expression:

$$J = p\left(\frac{1}{v} - 1\right)^{\theta},$$

where v can be equal with the product of v_0 and v_1 $(v = v_0 v_1)$.

Chapter 4: Mathematical Modeling of Stem Cell Transplantation in CML

The mathematical model

Based on system (1), we consider the following mathematical model for the post-transplant cell evolution

$$\begin{cases} x'(t) = \frac{ax(t)}{1+b_1(x(t)+z(t))+b_2y(t)} \frac{x(t)+y(t)}{x(t)+y(t)+gz(t)} - cx(t) \\ y'(t) = \frac{Ay(t)}{1+B(x(t)+y(t)+z(t))} \frac{x(t)+y(t)}{x(t)+y(t)+Gz(t)} - Cy(t) \\ z'(t) = \frac{az(t)}{1+b_1(x(t)+z(t))+b_2y(t)} \frac{z(t)}{z(t)+h(x(t)+y(t))} - cz(t), \end{cases} \tag{14}$$

where $x(t)$, $y(t)$ and $z(t)$ stand for normal host cells, abnormal host cells, and donor cells. The growth inhibitory factors

$$\frac{1}{1+g\frac{z}{x+y}}, \quad \frac{1}{1+G\frac{z}{x+y}} \quad \text{and} \quad \frac{1}{1+h\frac{x+y}{z}}$$

take into consideration the cell-cell interactions, quantitatively by the ratio $z/(x+y)$ and $(x+y)/z$ and qualitatively by parameters h, g and G which represents the intensity of the anti-host, anti-leukemia and anti-graft effects.

Existence, uniqueness and boundedness of solutions

Theorem: (Existence and uniqueness)

For any $t_0 \geq 0$ and $u_0 = (x_0, y_0, z_0) \in (0, +\infty)^3$, there is a unique saturated solution $u = u(\cdot, t_0, u_0) = (x, y, z)$ of system (14) which is defined on the whole semiline $[t_0, +\infty)$, is of class C^∞, with $x > 0$, $y > 0$ and $z > 0$ on $[t_0, +\infty)$, and satisfies the initial condition

$$u(t_0) = u_0.$$

Theorem: (Boundedness of solutions)

The solution $u = u(\cdot, t_0, u_0)$ is bounded on $[t_0, +\infty)$ for every $t_0 \geq 0$ and $u_0 \in (0, +\infty)^3$.

Steady states

The steady states of system (14) are obtained by solving the algebraic system

$$\frac{ax}{1+b_1x+b_2y+b_1z}\,\frac{x+y}{x+y+gz}-cx = 0 \tag{15a}$$

$$\frac{Ay}{1+B\left(x+y+z\right)}\,\frac{x+y}{x+y+Gz}-Cy = 0 \tag{15b}$$

$$\frac{az}{1+b_1x+b_2y+b_1z}\,\frac{z}{z+h\left(x+y\right)}-cz = 0 \tag{15c}$$

The solutions of the system (15a)-(15c) are the points

$$P_1(d,0,0);\quad P_2(0,D,0);\quad P_3(0,0,d);\quad P_4(x^*,y^*,0);$$
$$P_5(x^+,0,z^+);\quad P_6(0,y^{++},z^{++}) \text{ and } P_7(x^{\#},y^{\#},z^{\#}). \tag{16}$$

Here

$$x^*=\frac{b_2}{b_1-b_2}\left(\alpha d-D\right),\quad y^*=\frac{b_1}{b_1-b_2}\left(D-d\right), \tag{17}$$

$$x^+ = \frac{\frac{a}{c(1+\sqrt{gh})} - 1}{b_1\left(1+\sqrt{\frac{h}{g}}\right)}, \quad z^+ = \sqrt{\frac{h}{g}}x^+, \tag{18}$$

$$x^\# = \frac{b_1\left(1+\sqrt{\frac{g}{h}}\right)\left(1+G\sqrt{\frac{h}{g}}\right)\left(d-\frac{1}{b_1}\sqrt{gh}\right) - \left(1+\sqrt{gh}\right)\left(b_1+b_2\sqrt{\frac{g}{h}}\right)\left(D-\frac{G}{B}\sqrt{\frac{h}{g}}\right)}{(b_1-b_2)\left(1+\sqrt{gh}\right)\left(1+\sqrt{\frac{g}{h}}\right)\left(1+G\sqrt{\frac{h}{g}}\right)}, \tag{19}$$

$$y^\# = \frac{b_1}{b_1-b_2}\left(\frac{\left(1+\sqrt{gh}\right)\left(D-\frac{G}{B}\sqrt{\frac{h}{g}}\right) - \left(1+G\sqrt{\frac{h}{g}}\right)\left(d-\frac{1}{b_1}\sqrt{gh}\right)}{\left(1+G\sqrt{\frac{h}{g}}\right)\left(1+\sqrt{gh}\right)}\right) \tag{20}$$

and

$$z^\# = \frac{D-\frac{G}{B}\sqrt{\frac{h}{g}}}{\left(1+\sqrt{\frac{g}{h}}\right)\left(1+G\sqrt{\frac{h}{g}}\right)}, \tag{21}$$

while (y^{++}, z^{++}) represents the solution of the two-dimensional algebraic system

$$\begin{cases} \frac{A}{1+B(y+z)}\frac{y}{y+Gz} - C = 0 \\ \frac{a}{1+b_2y+b_1z}\frac{z}{z+hy} - c = 0. \end{cases} \tag{22}$$

We are only interested in solutions with non-negative components.

Admissible steady states in the chronic case:
We consider the system (14) in the chronic case. Hence

$$a > c, \quad A > C, \quad b_1 > b_2 > B \quad \text{and} \quad d < D < \alpha d. \tag{23}$$

See Theorem: (Admissible steady states in the chronic case).

Admissible steady states in the accelerated-acute case:
Let system (14) be in the accelerated-acute case, that is

$$a > c, \quad A > C, \quad b_1 > b_2 > B \quad \text{and} \quad \alpha d < D. \tag{24}$$

In this case we have the same conclusions like in the chronic case, except the point $P_4(x^*, y^*, 0)$ which is not admissible since $x^* < 0$, in view of the condition $\alpha d < D$.

Theorem: (Admissible steady states in the chronic case)

Let the assumptions (23) hold.
(i) The steady states $P_1(d,0,0)$, $P_2(0,D,0)$, $P_3(0,0,d)$, and $P_4(x^*,y^*,0)$ are admissible.
(ii) The steady state $P_5(x^+,0,z^+)$ is admissible if and only if

$$gh < \left(\frac{a}{c}-1\right)^2.$$

(iii) The steady state $P_6(0,y^{++},z^{++})$ is admissible if and only if

$$Gh < \left(\frac{A}{C}-1\right)\left(\frac{a}{c}-1\right).$$

(iv) The steady state $P_7(x^{\#},y^{\#},z^{\#})$ is admissible if and only if

$$Gh < \left(\frac{A}{C}-1\right)\sqrt{gh} < \left(\frac{A}{C}-1\right)\left(\frac{a}{c}-1\right),$$

and

$$\frac{1+\sqrt{gh}}{1+G\sqrt{\frac{h}{g}}} > \frac{d-\frac{1}{b_1}\sqrt{gh}}{D-\frac{G}{B}\sqrt{\frac{h}{g}}} > \frac{\left(1+\sqrt{gh}\right)\left(b_1+b_2\sqrt{\frac{g}{h}}\right)}{b_1\left(1+\sqrt{\frac{g}{h}}\right)\left(1+G\sqrt{\frac{h}{g}}\right)}.$$

Local stability of steady states

Theorem: (Stability analysis for the chronic phase of CML)

Let $a, b_1, b_2, c, A, B, C, g, G, h$ be positive parameters such that (23) holds. Then:
(a) $P_1(d, 0, 0)$ and $P_2(0, D, 0)$ are unstable equilibria;
(b) $P_3(0, 0, d)$ and $P_4\,(x^*, y^*, 0)$ given by *(17)*, are locally asymptotically stable equilibria;
(c) When $P_5\,(x^+, 0, z^+)$ given by *(18)* and $P_6\,(0, y^{++}, z^{++})$ given by *(22)* are admissible, they are unstable equilibria;
(d) When $P_7\,(x^\#, y^\#, z^\#)$ given by *(19)*, *(20)* and *(21)* is admissible, it is locally asymptotically stable if and only if

$$\delta_1 > 0,\ \ \delta_3 > 0 \ \text{ and } \ \delta_1\delta_2 > \delta_3,$$

where $\delta_1, \delta_2, \delta_3$ are given by

$$\delta_1 = -J_{11} - J_{22} - J_{33} = -tr(J), \quad \delta_2 = J_{11}J_{22} + J_{22}J_{33} + J_{11}J_{33} - J_{13}J_{31} - J_{32}J_{23} - J_{21}J_{12},$$
$$\delta_3 = -J_{11}J_{22}J_{33} - J_{21}J_{32}J_{13} - J_{31}J_{12}J_{23} + J_{13}J_{22}J_{31} + J_{23}J_{32}J_{11} + J_{33}J_{12}J_{21} = -\det(J)$$

and $J_{ij},\ i, j = 1, 2, 3$ are the elements of the Jacobian matrix calculated at $(x^\#, y^\#, z^\#)$.

Recall that the equilibrium $P_5\left(x^+, 0, z^+\right)$ is admissible if and only if

$$gh < \left(\frac{a}{c} - 1\right)^2,$$

and the equilibrium $P_6\left(0, y^{++}, z^{++}\right)$ is admissible if and only if

$$Gh < \left(\frac{A}{C} - 1\right)\left(\frac{a}{c} - 1\right).$$

Hence, only one or both $P_5\left(x^+, 0, z^+\right)$ and $P_6\left(0, y^{++}, z^{++}\right)$ could be admissible. When they are admissible, they are unstable and their local stability on manifolds is specified by the following proposition.

Proposition: (Local stability on manifolds)

Assume that $h \geq 1$. Then
(1) If $P_5\left(x^+, 0, z^+\right)$ is admissible and $P_6\left(0, y^{++}, z^{++}\right)$ is not, then $P_5\left(x^+, 0, z^+\right)$ has a two-dimensional locally stable invariant manifold.
(2) If $P_6\left(0, y^{++}, z^{++}\right)$ is admissible and $P_5\left(x^+, 0, z^+\right)$ is not, then $P_6\left(0, y^{++}, z^{++}\right)$ has a two-dimensional locally stable invariant manifold.
(3) Assume that both $P_5\left(x^+, 0, z^+\right)$ and $P_6\left(0, y^{++}, z^{++}\right)$ are admissible.

Then
(a) If $f(\sqrt{\frac{g}{h}}) > 0$, where

$$f\left(\sqrt{\frac{g}{h}}\right) = \frac{A}{BC}\frac{\sqrt{gh}}{\sqrt{gh}+Gh} - \frac{a}{b_2 c}\frac{\sqrt{gh}+h}{\sqrt{gh}+\alpha h}\frac{1}{1+\sqrt{gh}} - \frac{1}{B} + \frac{1}{b_2}\frac{\sqrt{gh}+h}{\sqrt{gh}+\alpha h},$$

then $P_5\left(x^+, 0, z^+\right)$ has a one-dimensional locally stable invariant manifold, and $P_6\left(0, y^{++}, z^{++}\right)$ has a two-dimensional locally stable invariant manifold.
(b) If $f(\sqrt{\frac{g}{h}}) < 0$ and

$$\frac{(b_1-b_2)\sqrt{gh}}{b_1 b_2(\sqrt{gh}+\alpha h)}\left(\frac{a}{c}\frac{1}{1+\sqrt{gh}} - 1\right) > -f\left(\sqrt{\frac{g}{h}}\right),$$

then $P_5\left(x^+, 0, z^+\right)$ has a one-dimensional locally stable invariant manifold, and $P_6\left(0, y^{++}, z^{++}\right)$ has a one-dimensional locally stable invariant manifold.
(c) If $f(\sqrt{\frac{g}{h}}) < 0$ and

$$\frac{(b_1-b_2)\sqrt{gh}}{b_1 b_2(\sqrt{gh}+\alpha h)}\left(\frac{a}{c}\frac{1}{1+\sqrt{gh}} - 1\right) < -f\left(\sqrt{\frac{g}{h}}\right),$$

then $P_5\left(x^+, 0, z^+\right)$ has a two-dimensional locally stable invariant manifold, and $P_6\left(0, y^{++}, z^{++}\right)$ has a one-dimensional locally stable invariant manifold.

Numerical simulations of the model

Numerical simulations in the chronic case:

Case (a): Assume that $P_5\left(x^+, 0, z^+\right)$ is not admissible and $P_6\left(0, y^{++}, z^{++}\right)$ is admissible. Consider the following values of the parameters:

$$a = 0.23, \quad b_1 = 2.2 \times 10^{-8}, \quad b_2 = 1.1 \times 10^{-8}, \quad c = 0.01,$$
$$A = 0.33, \quad B = 5.5 \times 10^{-9}, \quad C = 0.03,$$
$$g = 25, \quad G = 4, \quad h = 20,$$

for which

$$d = 10^9, \quad D = 1.81 \times 10^9, \quad \alpha d = 2 \times 10^9,$$

and the following conditions hold

$$a > c, \quad A > C, \quad b_1 > b_2 > B \quad \text{and} \quad d < D < \alpha d \quad \text{(chronic case)}.$$

Also, the computations

$$gh = 500 > \left(\frac{a}{c} - 1\right)^2 = 484 \quad \text{and} \quad Gh = 80 < \left(\frac{A}{C} - 1\right)\left(\frac{a}{c} - 1\right) = 220,$$

confirm that $P_5\left(x^+, 0, z^+\right)$ is not admissible and $P_6\left(0, y^{++}, z^{++}\right)$ is admissible. In addition, the condition for the admissibility of $P_7\left(x^{\#}, y^{\#}, z^{\#}\right)$ does not hold since

$$\begin{aligned} \frac{1+\sqrt{gh}}{1+G\sqrt{\frac{h}{g}}} &= 5.10313 > \frac{d-\frac{1}{b_1}\sqrt{gh}}{D-\frac{G}{B}\sqrt{\frac{h}{g}}} = -0.01404 \\ &\not> \frac{\left(1+\sqrt{gh}\right)\left(b_1+b_2\sqrt{\frac{g}{h}}\right)}{b_1\left(1+\sqrt{\frac{g}{h}}\right)\left(1+G\sqrt{\frac{h}{g}}\right)} = 3.75625. \end{aligned}$$

Hence, for this simulation, we have no $P_5\left(x^+, 0, z^+\right)$ and $P_7\left(x^{\#}, y^{\#}, z^{\#}\right)$ as admissible equilibria, but there exists the admissible equilibrium $P_6\left(0,\ 1.85935\times 10^7,\ 3.48656\times 10^7\right)$ for which the eigenvalues of the corresponding Jacobian matrix are

$$-0.005412297301854,\quad 0.034764565551854,\quad -0.007563470039000.$$

Thus $P_6\left(0, y^{++}, z^{++}\right)$ is an unstable equilibrium.

The next figure illustrates the phase portrait of system (14).

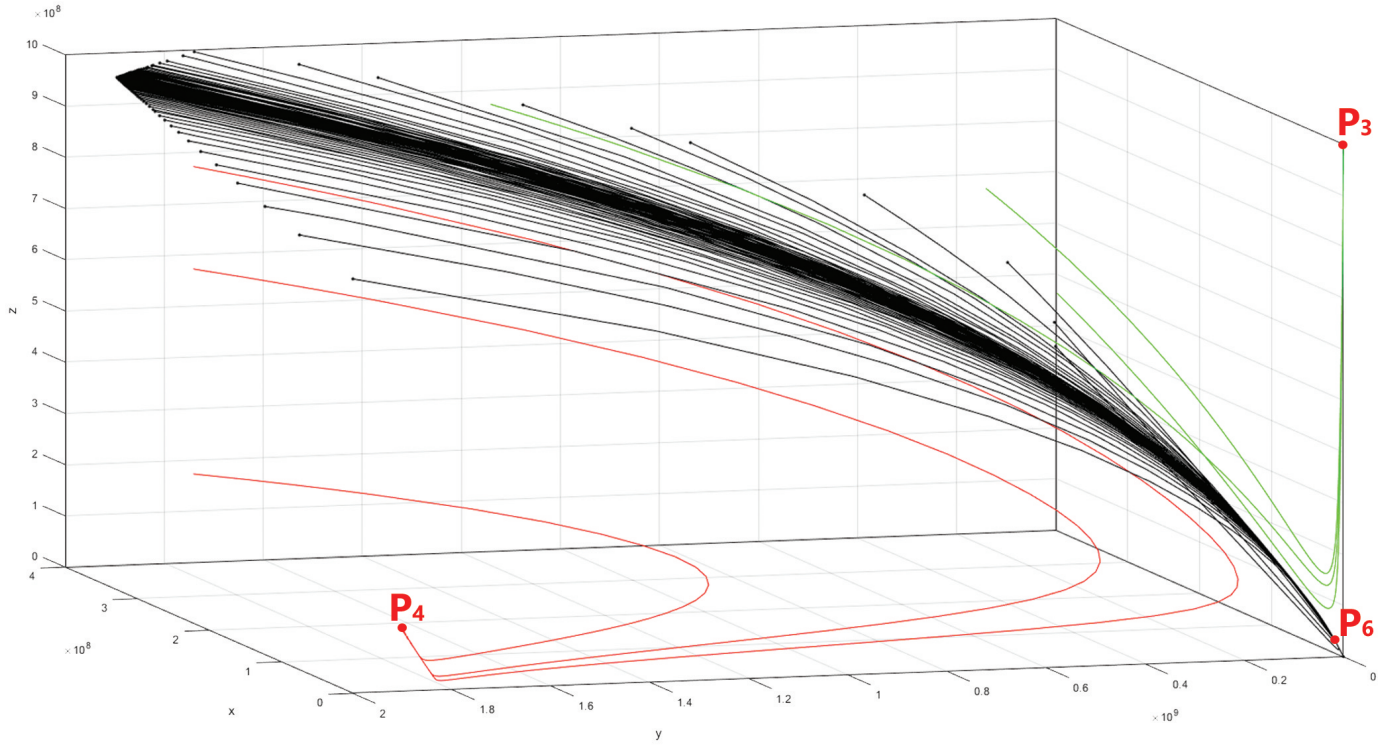


Figure: Phase portrait of system (14). In black it is represented the separation surface between the basin of attraction of the 'good' equilibrium $P_3(0, 0, 10^9)$ and the basin of attraction of the 'bad' equilibrium $P_4(1.818181818 \times 10^8,\ 1.636363636 \times 10^9,\ 0)$. (Matlab code source can be found in Appendix)

Numerical simulations in the accelerated-acute case:

Case (a): Assume that $P_4\left(x^+, 0, z^+\right)$ is not admissible and $P_5\left(0, y^{++}, z^{++}\right)$ is admissible. The phase portrait of system (14).

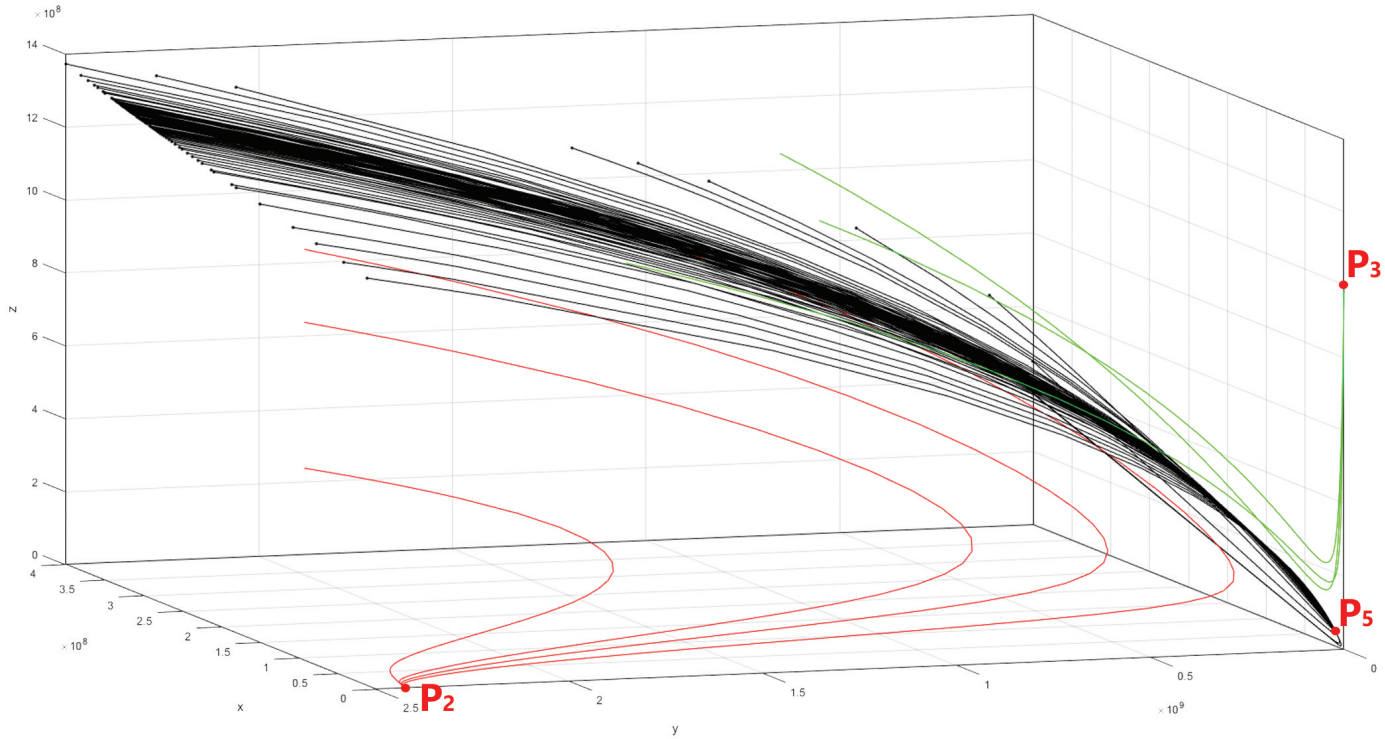


Figure: In black it is represented the separation surface between the basin of attraction of the 'good' equilibrium $P_3(0, 0, 10^9)$ and the basin of attraction of the 'bad' equilibrium $P_2(0, 2.424242423 \times 10^9, 0)$.


L. Parajdi, *Modeling the treatment of tumor cells in a solid tumor*, J. Nonlinear Sci. Appl. **7** (2014), 188–195.


L.G. Parajdi and R. Precup, *Analysis of a planar differential system arising from hematology*, Stud. Univ. Babeș-Bolyai Math. **63** (2018), 235–244.


R. Precup, D. Dima, C. Tomuleasa, M.A. Șerban and **L.G. Parajdi**, *Theoretical models of hematopoietic cell dynamics related to bone marrow transplantation*, In Frontiers in Stem Cell and Regenerative Medicine Research, Bentham Science Publishers-Sharjah, **8** (2018), 202–241.


L.G. Parajdi, *Stability of the equilibria of a dynamic system modeling stem cell transplantation*, Springer: Ricerche mat (2019).


L.G. Parajdi, R. Precup, D. Dima, V. Moisoiu and C. Tomuleasa, *Theoretical basis of optimal therapy for individual patients in chronic myeloid leukemia. A mathematical approach*, Journal of Interdisciplinary Mathematics (2019), 1-22.


V. Moisoiu, P. Teodorescu, **L. Parajdi**, S. Pasca, M. Zdrenghea, D. Dima, R. Precup, C. Tomuleasa and S. Soverini, *Assessing Measurable Residual Disease in Chronic Myeloid Leukemia. BCR-ABL1 IS in the Avant-Garde of Molecular Hematology*, Frontiers in Oncology, **9**(863) (2019), 1–8.

L.G. Parajdi, R. Precup, E.A. Bonci and C. Tomuleasa, *A mathematical model of the transition from normal hematopoiesis to the chronic and accelerated acute stages in myeloid leukemia*, MDPI: Mathematics, (2020), 8, 376.

⋆ ⋆ ⋆

F. Michor, T.P. Hughes, Y. Iwasa, S. Branford, N.P. Shah, C.L. Sawyers and M.A. Nowak, *Dynamics of chronic myeloid leukaemia*, Nature **435** (2005), 1267–1270.

D. Dingli and F. Michor, *Successful therapy must eradicate cancer stem cells*, Stem Cells **24** (2006), 2603–2610.

A. Cucuianu and R. Precup, *A hypothetical-mathematical model of acute myeloid leukemia pathogenesis*, Comput. Math. Methods Med. **11** (2010), 49–65.

R. Precup, M.A. Şerban, D. Trif and A. Cucuianu, *A planning algorithm for correction therapies after allogeneic stem cell transplantation*, J. Math. Model. Algor. **11** (2012), 309–323.

Q. He, J. Zhu, D. Dingli, J. Foo and K.Z. Leder, *Optimized treatment schedules for chronic myeloid leukemia*, PLoS Comput. Biol. **12**(10) (2016), e1005129.

Thank you for your attention !